Original Article

Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study

Address for correspondence:
Dr. Sameer N Desai, Department of Anaesthesiology, Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Sattur, Dharwad - 580 009, Karnataka, India.
E-mail: sameeranaes@gmail.com

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Sameer N Desai, Santhoshi V Badiger, Shreesha B Tokur[1], Prashanth A Naik[1]

Departments of Anaesthesiology and [1]Orthopaedics, Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka, India

ABSTRACT

Background: Transdermal buprenorphine, which is used in chronic pain management, has rarely been studied for use in acute pain management. The aim of this study was to compare the safety and efficacy of transdermal buprenorphine patch to oral tramadol for post-operative analgesia, following proximal femur surgeries. **Methodology:** Fifty adult patients undergoing surgery for hip fracture under spinal anaesthesia were included in this study. One group (Group TDB) received transdermal buprenorphine 10 mcg/h patch applied a day before the surgery and other group received oral tramadol 50 mg three times a day for analgesia (Group OT). They were allowed to take diclofenac and paracetamol tablets for rescue analgesia. Pain scores at rest, on movement, rescue analgesic requirement and side effects were compared between the groups over 7 days. Chi-square and independent sample *t*-test were used for categorical and continuous variables, respectively. **Results:** Resting pain scores and pain on movement were significantly lower in TDB Group on all 7 days starting from 24 h post-operatively. Rescue analgesic requirement was significantly lower in TDB Group compared to OT Group. All the patients needed rescue analgesic in OT Group whereas 68% of the patients needed the same in TDB Group. Incidence of vomiting was less and satisfaction scores were much higher in TDB Group as compared to OT Group (79% vs. 66%, $P < 0.001$). **Conclusion:** Transdermal buprenorphine can be safely used for post-operative analgesia and is more efficacious in reducing post-operative pain after 24 hours, with fewer side effects when compared to oral tramadol.

Key words: Buprenorphine, hip fractures, post-operative pain, tramadol, transdermal patch

INTRODUCTION

Hip fractures are commonly seen fractures in the elderly and are associated with moderate to severe pain.[1] These patients need good post-operative analgesia for early rehabilitation and mobilisation. Peripheral nerve blockade used for anaesthesia is rarely effective beyond the first post-operative night.[2] Approximately 40% of patients presenting with hip fracture have at least moderate renal dysfunction; hence, non-steroidal anti-inflammatory agents are relatively contraindicated in these patients.[3] Opioids and tramadol have to be used with caution in patients with renal dysfunction.[2] Buprenorphine, which is metabolised in the liver, has been shown to be safe even in patients with end-stage renal failure.[4] Transdermal buprenorphine, which releases the analgesic over a period of 7 days, is used to treat a variety of chronic pain conditions.[5] There are very few studies demonstrating its utility in post-operative

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pain. We could not find any study comparing the use of transdermal buprenorphine for the post-operative analgesia to conventionally used analgesics. The aim of this study was to compare the safety and efficacy of transdermal buprenorphine patch to conventionally used analgesic, oral tramadol, for post-operative analgesia following proximal femur surgeries.

METHODOLOGY

After obtaining the Institute's Ethical Committee approval, this prospective, randomised study was carried out from January to December 2015. The study was registered with Clinical Trial Registry of India (CTRI) with reference number: REF/2015/03/008677. Patients in the age group of 18–80 years with American Society of Anesthesiologists Physical Status I–III undergoing surgery for proximal femur fractures under spinal anaesthesia were included in this study. Patients who had polytrauma with any other fractures, obese (body mass index >35) and those with hepatic or renal impairment or suffering from myasthenia gravis, delirium tremens and dermatitis at the patch application site were excluded from the study.

A total of fifty patients were divided into either transdermal buprenorphine patch group (Group TDB) or oral tramadol group (Group OT) using a randomisation table. The patients were aware of the group they belonged to (by looking at buprenorphine patch or tramadol tablets they needed to take). However, the person assessing pain and satisfaction score was unaware of the group the patient belonged. Hence, this was a single-blinded study. The patients were explained about the study drugs, post-operative pain treatment options and pain score assessment, a day before the surgery. For the patients in the TDB Group, a buprenorphine patch of 10 mcg/h was applied to the upper outer arm, a day before the surgery (effective serum concentration for TDB is achieved after 12–24 h).[6] The other group of patients continued to receive 50 mg of tramadol tablet pre-operatively. All the patients received 0.25 mg of alprazolam night before the surgery. Spinal anaesthesia was administered with 3 ml of hyperbaric bupivacaine 0.5%, along with 30 mcg of clonidine. The patients in TDB Group did not receive any other analgesic (except buprenorphine patch) as a routine, whereas patients in Group OT received oral tramadol tablets 50 mg three times a day. Post-operatively, pain was assessed using visual analogue scores (0–100), at rest and with movement at the following time periods: pre-operatively and 4, 12 and 24 h post-operatively and then daily for 7 days. If patient's pain score was 4 or higher, then they took rescue analgesic, diclofenac tablets 50 mg up to two times a day. If the pain persisted despite this, then they received 1 g of oral paracetamol up to three times a day. Despite these, if pain scores were higher, physician was allowed to administer 50 mg of intramuscular pethidine. The ability to move the limb during the physiotherapy (if limited by pain) was noted post-operatively. The patient satisfaction with post-operative pain treatment was assessed with score of 0–100. Side effects such as giddiness, drowsiness, post-operative nausea and vomiting (PONV), constipation, respiratory depression and patch site redness were noted.

Initial pilot study indicated that 100% of patients in tramadol group needed rescue analgesics. We calculated that for 25% reduction in the need for rescue analgesics with α error of 0.05 and 80% power, we need to include 21 patients in each group. Therefore, we studied 25 patients in each group considering for possible dropouts. Categorical data such as type of surgeries and number of patients needing rescue analgesics were compared using Chi-square test. Continuous variables such as pain scores, satisfaction scores and number of tablets consumed were compared using independent sample *t*-test. Statistical analyses were performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation or as the number of patients and percentages. Value of $P < 0.05$ was considered statistically significant.

RESULTS

There were no differences between the groups for age, sex, site of fracture (intra- or extra-capsular), type of surgery (hemiarthroplasty, percutaneous nailing or dynamic hip screw), duration of surgery or anaesthesia [Table 1]. Resting pain scores were not significantly different between the groups before operation, at 4 and 12 h after the operation. However, pain scores were significantly lower in TDB Group on all 7 days starting from 24 h post-operatively [Figure 1]. Similarly, pain scores on movement were not significant between the groups up to 24 h post-operatively and were consistently lower in TDP Group from the 2nd to 7th day as compared to OT Group [Figure 2]. All the patients (100%) needed rescue analgesic in OT Group, whereas only 68% of the patients in TDB Group needed the same ($P < 0.01$).

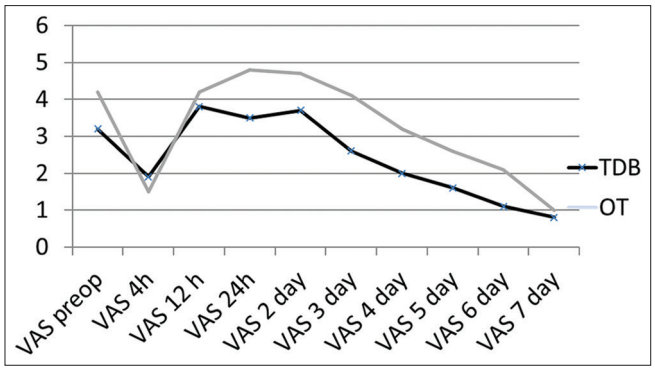

Figure 1: Pain score at rest visual analogue scores 0–10

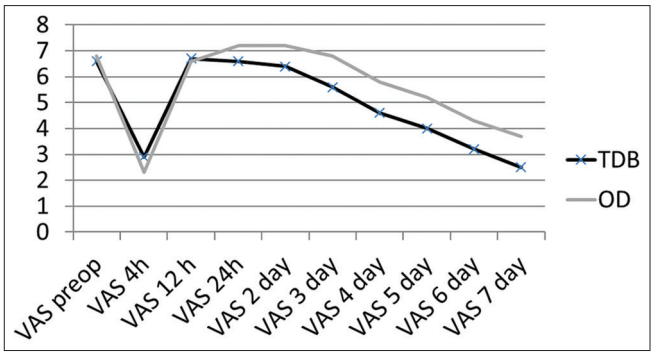

Figure 2: Pain score on movement visual analogue scores 0–10

Table 1: Patient characteristics, surgery and anaesthetic data

Parameter	Group transdermal buprenorphine	Group oral tramadol	*P*
n	25	25	
Age (year)	59.9±12.8	63.7±14.4	0.33
Sex, male/female	11/14	14/11	0.57
ASA Grades I/II/II	8/12/5	9/11/5	0.95
Site of fracture: Extracapsular/intracapsular	19/6	21/4	0.14
Surgery done: PFN/DHS/ hemi-arthroplasty + AMP	17/2/6	15/6/4	0.16
Anaesthesia duration (min)	139±32	132±30	0.43
Duration of surgery (min)	106±27	104±30	0.80

Values are mean±SD or the number of patients. ASA – American Society of Anaesthesiologists; SD – Standard deviation; DHS – Dynamic hip screw; PFN – Proximal femoral nail; AMP – Austin Moore prosthesis

Total number of diclofenac tablets used as rescue analgesic was lower in TDB Group [Table 2]. Overall side effects were much lower in TDB Group compared to tramadol group. Incidence of PONV was particularly high with oral tramadol compared to buprenorphine group ($P < 0.01$). None of the patients in either group had significant respiratory depression or sedation. None of the patients in transdermal buprenorphine had any skin rash. Satisfaction scores were much higher for TDB Group compared to Group OT (79 ± 8 vs. 66 ± 11, $P < 0.001$).

DISCUSSION

In this study, we used the transdermal buprenorphine patch for the management of post-operative pain and compared it with traditionally used analgesic, oral tramadol. We noted that patients using transdermal buprenorphine patch had lower pain scores (both at rest and on movement), used fewer number of rescue analgesic tablets, had lower incidence of vomiting as side effect and had higher satisfaction scores compared to those receiving tramadol for post-operative analgesia.

Tramadol is a centrally acting analgesic with weak opioid agonist. Its safety is well established by the fact that the clinically relevant respiratory depression is not seen with tramadol and it has low dependence and abuse potential. All these properties make tramadol as the ideal drug for the management of post-operative pain. Hence, tramadol is one of the most commonly used analgesics in post-operative period.[7] Oral tramadol has good bioavailability (70%–90%); hence, oral tramadol has been used for providing post-operative analgesia.[8,9] However, it has lower efficacy in pain management, high incidence of PONV. It should be used cautiously in patients with renal failure due to risk of accumulation.[2]

Buprenorphine is a potent centrally acting opioid analgesic, which has been available for use in the clinical practice in a variety of settings for 30 years.[10] Because of its low bioavailability, it is not useful by oral route. The physicochemical properties of buprenorphine (low molecular weight, high lipophilicity and high affinity for the μ-opioid receptor) make it a well-suited drug for transdermal delivery. The availability of the transdermal preparation, which releases buprenorphine over a 7-day period, has led to re-emergence of the drug. Transdermal buprenorphine has been used in the management of chronic cancer and non-cancer pains for few years.[11] It has been shown to be safe for long-term use even in elderly without much change in pharmacokinetics.[12,13] It can be safely used in patients with decreased renal reserve and even end-stage renal failure.[4] Despite these favourable properties, transdermal buprenorphine has been rarely studied in post-operative settings.

Transdermal buprenorphine has been compared to tramadol and co-codamol for non-cancer chronic pain such as osteoarthritis pain.[14] They have noted that transdermal buprenorphine to be non-inferior to these

Table 2: Rescue analgesic requirement and side effect profile

Analgesics used	Group transdermal buprenorphine	Group oral tramadol	*P*
Average number of diclofenac tablets consumed in 7 post-operative days	2.4±2.2	6.6±3.0	0.01
Average number of paracetamol tablets consumed in 7 post-operative days	0.68±2.2	1.9±3.7	0.15
Number of patients where rescue analgesia was needed in 7 days (%)	17 (68)	25 (100)	0.01
Satisfaction score in percentage	79±8	66±11	0.01
Side effects			
Nausea and vomiting	1	8	0.01
Constipation	1	3	
Headache	0	2	

oral analgesics in terms of analgesic efficacy. These studies noted reduced use of rescue analgesia and better patient satisfaction with buprenorphine patch when compared to the other oral analgesics.

There are very few studies using transdermal buprenorphine for post-operative analgesia.[15-17] All these were descriptive studies indicating the beneficial utility of transdermal buprenorphine for providing post-operative pain relief. Privetra and Guzzetta in two separate descriptive studies used 35 mcg/h of TDB for patients undergoing shoulder and upper femur surgeries.[16,17] They noted satisfactory analgesia 24 h after the surgery in almost 75% patients. They concluded that TDB can be used safely for providing effective post-operative analgesia with high satisfaction rating by the patients. Setti *et al*. used 17.5, 35, 52.5 mcg/h of TDB patches to patients undergoing open gynaecologic surgeries, providing intravenous morphine and ketorolac as rescue analgesics.[15] They found that the consumption of rescue analgesia was inversely correlated to the TDB dosage. Increasing TDB doses were not associated with an increased incidence of side effects. They concluded that TDB is a safe and feasible approach to moderate post-operative pain management. We used much lower dose of TDB 10 mcg/h in our study and noticed that 68% of the patients needed some rescue analgesia. Previous studies with 35 mcg/h dose have noted that the need for rescue analgesics in only 25% of patients.

Another study comparing transdermal fentanyl 25 mcg/h to transdermal buprenorphine 10 mcg/h noted that both fentanyl and buprenorphine are safe and effective for post-operative pain but fentanyl is more efficacious than buprenorphine.[18] We could not find any study comparing the use of TDB to oral analgesics in the management of post-operative pain.

Transdermal system allows passive transdermal diffusion of medication over a prolonged period while maintaining constant plasma levels of the drug. It is non-invasive, easily administered, has a sustained effect and can provide long-term pain relief.[19] Studies have shown that multiple daily dosing can be inconvenient and may decrease compliance and fail to provide sufficient around-the-clock analgesia.[20,21] Analgesic gaps are less likely with transdermal system. Previous studies have demonstrated effective analgesia when transdermal fentanyl was used for management of post-operative pain following orthopaedic, abdominal, gynaecologic surgeries.[22,23] Even though transdermal delivery has been shown to be useful, it is not preferred for post-operative analgesia. That is because few studies noted that even though requirement of rescue analgesia is reduced, but it is not completely eliminated. Hence, they concluded that due to long latency for onset and sustained effects makes transdermal delivery not a good choice for post-operative analgesia and it will not be an alternative for patient-controlled analgesia (PCA).[24] We feel that criticism of transdermal system, namely, slow onset and sustained effect, making it inferior mode of analgesic delivery compared to PCA in the post-operative period may be true. However, it may be still superior to other conventionally used routes of analgesic delivery in the post-operative period.

We noted very low incidence of side effects, particularly PONV with TDB. These side effects incidence are similar to a large post-marketing surveillance study of buprenorphine, where they have noted low incidence of nausea (4%), vomiting (1.6%) and constipation (1.0%).[25]

One of the limitations of the present study is that it was single blinded, patients knew to which study group they belonged to. Second, we used single fixed

dose of 10 mcg/h patch which is lower than commonly recommended dose. Hence, more studies with double blinding (using a placebo patch) and higher dose buprenorphine are advisable in the future.

CONCLUSION

Transdermal buprenorphine can be safely used for post-operative analgesia and is more efficacious in reducing post-operative pain, with less side effects and better satisfaction score when compared to oral tramadol.

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Conflicts of interest

There are no conflicts of interest.

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